**Search Results -**

| Terms | Documents |
|---|---|
| l6 and infarction | 11 |

**Database:** US Patents Full-Text Database; JPO Abstracts Database; EPO Abstracts Database; Derwent World Patents Index; IBM Technical Disclosure Bulletins

Refine Search: l6 and infarction Clear

## Search History

**Today's Date: 11/27/2000**

| DB Name | Query | Hit Count | Set Name |
|---|---|---|---|
| USPT,JPAB,EPAB,DWPI,TDBD | l6 and infarction | 11 | L7 |
| USPT,JPAB,EPAB,DWPI,TDBD | Akt or (protein adj kinase adj B) | 360 | L6 |
| USPT,JPAB,EPAB,DWPI,TDBD | Akt$ | 75826 | L5 |
| USPT,JPAB,EPAB,DWPI,TDBD | l3 and apopto$ | 5 | L4 |
| USPT,JPAB,EPAB,DWPI,TDBD | Walsh-K$.in. | 121 | L3 |
| USPT,JPAB,EPAB,DWPI,TDBD | infarction and l1 | 7 | L2 |
| USPT,JPAB,EPAB,DWPI,TDBD | adminis$ near Bcl-2 | 13 | L1 |

Trying 3106016892...Open

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LOGINID:ssspta1642gxn
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| NEWS 3 | Aug 24 | TABULATE Now Available in More STN Databases |
| NEWS 4 | Aug 28 | MEDLINE from 1958 to Date - Only on STN |
| NEWS 5 | Sep 7 | DGENE GETSIM ALERT: Similarity Current-Awareness Searching of Biosequences |
| NEWS 6 | Sep 11 | Textile Technology Digest (TEXTILETECH) now available on STN |
| NEWS 7 | Sep 21 | KKF renamed DKILIT |
| NEWS 8 | Sep 29 | The Philippines Inventory of Chemicals and Chemical Substances (PICCS) has been added to CHEMLIST |
| NEWS 9 | Oct 27 | New Extraction Code PAX now available in Derwent Files |
| NEWS 10 | Oct 27 | SET ABBREVIATIONS and SET PLURALS extended in Derwent World Patents Index files |
| NEWS 11 | Oct 27 | Patent Assignee Code Dictionary now available in Derwent Patent Files |
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FILE 'HOME' ENTERED AT 09:44:20 ON 27 NOV 2000

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| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| FULL ESTIMATED COST | 0.15 | 0.15 |

FILE 'MEDLINE' ENTERED AT 09:44:28 ON 27 NOV 2000

FILE 'CANCERLIT' ENTERED AT 09:44:28 ON 27 NOV 2000

FILE 'BIOSIS' ENTERED AT 09:44:28 ON 27 NOV 2000
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FILE 'EMBASE' ENTERED AT 09:44:28 ON 27 NOV 2000


FILE 'SCISEARCH' ENTERED AT 09:44:28 ON 27 NOV 2000


=> s akt or protein kinase B or PKB

4 FILES SEARCHED...
L1 6893 AKT OR PROTEIN KINASE B OR PKB

=> s walsh-K?/au

L2 3320 WALSH-K?/AU

=> s l1 and l2

L3 55 L1 AND L2

=> s l1 and infarction

L4 17 L1 AND INFARCTION

=> dup rem l4

PROCESSING COMPLETED FOR L4
L5 10 DUP REM L4 (7 DUPLICATES REMOVED)

=> d ibib abs 1-10

L5 ANSWER 1 OF 10 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2000287431 MEDLINE
DOCUMENT NUMBER: 20287431
TITLE: Signaling properties and functions of two distinct cardiomyocyte protease-activated receptors.
AUTHOR: Sabri A; Muske G; Zhang H; Pak E; Darrow A; Andrade-Gordon P; Steinberg S F
CORPORATE SOURCE: Department of Pharmacology, Columbia University, New York, NY 10032, USA.
CONTRACT NUMBER: HL-49537 (NHLBI)
SOURCE: CIRCULATION RESEARCH, (2000 May 26) 86 (10) 1054-61.
Journal code: DAJ. ISSN: 0009-7330.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200008
ENTRY WEEK: 20000804
AB Previous studies have established that cardiomyocytes express protease-activated receptor (PAR)-1, a high-affinity receptor for thrombin, which is also activated by the tethered-ligand domain sequence (SFLLRN) and which promotes inositol trisphosphate accumulation, stimulates extracellular signal-regulated protein kinase, and modulates

contractile function. A single previous report identified PAR-1 as a hypertrophic stimulus, but there have been no subsequent investigations of the mechanism. This study reveals the coexpression of PAR-1 and PAR-2 (a second PAR, which is activated by trypsin/tryptase but not thrombin) by Northern blot analysis and compares their signaling properties in neonatal rat ventricular cardiomyocytes. SFLLRN and SLIGRL (an agonist peptide for PAR-2) promote inositol trisphosphate accumulation, stimulate mitogen-activated protein kinases (extracellular signal-regulated protein kinase and p38-mitogen-activated protein kinase), elevate calcium concentration, and increase spontaneous automaticity. SFLLRN (but not SLIGRL) also activates c-Jun NH(2)-terminal kinase and **AKT**. In keeping with their linkage to pathways that have been associated with growth and/or survival, SFLLRN and SLIGRL both induce hypertrophy. However, PAR agonists promote cell elongation, a morphology that is distinct from the uniform increase in cell dimension induced by alpha(1)-adrenergic receptor activation. These studies provide novel evidence that cardiomyocytes coexpress 2 functional PARs, which link to a common set of signals that culminate in changes in contractile function and hypertrophic growth. PAR actions may assume clinical importance in the border zone surrounding an **infarction**, where local proteolysis of PARs by serine proteases generated during inflammatory or thrombogenic pathways would elevate calcium concentration (setting the stage for arrhythmias), promote hypertrophic growth, and/or influence cardiomyocyte survival.

L5 ANSWER 2 OF 10 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000302028 EMBASE
TITLE: Ischemic preconditioning activates phosphatidylinositol-3-kinase upstream of protein kinase C.
AUTHOR: Tong H.; Chen W.; Steenbergen C.; Murphy E.
CORPORATE SOURCE: H. Tong, Mail drop D2-03, NIEHS, Research Triangle Park, NC 27709, United States. tong@niehs.nih.gov
SOURCE: Circulation Research, (18 Aug 2000) 87/4 (309-315). Refs: 37
ISSN: 0009-7330 CODEN: CIRUAL
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The present study is designed to test whether phosphatidylinositol 3-kinase (PI3-kinase) has a role in the signaling pathway in ischemic preconditioning (PC) and whether it is proximal or distal to protein kinase C (PKC). Before 20 minutes of global ischemia, Langendorff-perfused rat hearts were perfused for 20 minutes (control); preconditioned with 4 cycles of 5-minute ischemia and 5-minute reflow (PC); treated with either wortmannin (WM) or LY 294002 (LY), each of which is a PI3-kinase inhibitor, for 5 minutes before and throughout PC; treated with 1,2-dioctanoyl-sn-glycerol (DOG), an activator of PKC for 10 minutes (DOG); treated identically to the DOG group except with WM added 10 minutes before and during perfusion with DOG; or treated with either WM or LY for 25 minutes. Recovery of left ventricular developed pressure (LVDP; percentage of initial preischemic LVDP), measured after 30 minutes of

reflow, was improved by PC (72.+-.2% versus 36.+-.4% in control; P<0.001),
and this was blocked by WM and LY (41.+-.4% and 43.+-.5%, respectively; P<0.05 compared with PC). DOG addition improved postischemic LVDP (67.+-.6%; P<0.001 compared with control), but in contrast to its effect on PC, WM did not completely eliminate the protective effect of DOG (52.+-.4%; P>0.05 compared with DOG; P<0.05 compared with control). PC induced phosphorylation of **protein kinase B**
and translocation of PKC.epsilon., and it increased NO production, and these effects were blocked by WM, which suggests a role for PI3-kinase in PC upstream of PKC and NO.

L5 ANSWER 3 OF 10 SCISEARCH COPYRIGHT 2000 ISI (R)
ACCESSION NUMBER: 2000:187844 SCISEARCH
THE GENUINE ARTICLE: 289GX
TITLE: Calcineurin-mediated hypertrophy protects cardiomyocytes from apoptosis in vitro and in vivo - An apoptosis-independent model of dilated heart failure
AUTHOR: DeWindt L J; Lim H W; Taigen T; Wencker D; Condorelli G; Dorn G W; Kitsis R N; Molkentin J D (Reprint)
CORPORATE SOURCE: CHILDRENS HOSP, MED CTR, DIV MOL CARDIOVASC BIOL, DEPT PEDIAT, 3333 BURNET AVE, CINCINNATI, OH 45229 (Reprint); CHILDRENS HOSP, MED CTR, DIV MOL CARDIOVASC BIOL, DEPT PEDIAT, CINCINNATI, OH 45229; UNIV CINCINNATI, DEPT PEDIAT, CINCINNATI, OH 45221; UNIV CINCINNATI, DEPT CARDIOL, CINCINNATI, OH; ALBERT EINSTEIN COLL MED, DEPT MED, BRONX, NY 10467; ALBERT EINSTEIN COLL MED, DEPT CELL BIOL, BRONX, NY 10467; THOMAS JEFFERSON UNIV, KIMMEL CANC CTR, PHILADELPHIA, PA; THOMAS JEFFERSON UNIV, DEPT MICROBIOL, PHILADELPHIA, PA; THOMAS JEFFERSON UNIV, DEPT IMMUNOL, PHILADELPHIA, PA
COUNTRY OF AUTHOR: USA
SOURCE: CIRCULATION RESEARCH, (18 FEB 2000) Vol. 86, No. 3, pp. 255-263.
Publisher: LIPPINCOTT WILLIAMS & WILKINS,. 530 WALNUT ST, PHILADELPHIA, PA 19106-3621.
ISSN: 0009-7330.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 50

*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB We have previously shown that the calcium-calmodulin-regulated phosphatase calcineurin (PP2B) is sufficient to induce cardiac hypertrophy
that transitions to heart failure in transgenic mice. Given the rapid onset of heart failure in these mice, we hypothesized that calcineurin signaling would stimulate myocardial cell apoptosis. However, utilizing multiple approaches, we determined that calcineurin-mediated hypertrophy protected cardiac myocytes from apoptosis, suggesting a model of heart failure that is independent of apoptosis. Adenovirally mediated gene transfer of a constitutively active calcineurin cDNA (AdCnA) was performed
in cultured neonatal rat cardiomyocytes to elucidate the mechanism whereby
calcineurin affected myocardial cell viability. AdCnA infection, which induced myocyte hypertrophy and atrial natriuretic factor expression, protected against apoptosis induced by 2-deoxyglucose or staurosporine, as

assessed by terminal deoxynucleotidyltransferase;mediated dUTP nick end labeling (TUNEL) labeling, caspase-3 activation, DNA laddering, and cellular morphology. The level of protection conferred by AdCnA was similar to that of adenoviral Bcl-x(L) gene transfer or hypertrophy induced by phenylephrine. In vivo, failing hearts from calcineurin-transgenic mice did not demonstrate increased TUNEL labeling and, in fact, demonstrated a resistance to ischemia/reperfusion-induced apoptosis, We determined that the mechanism whereby calcineurin afforded protection from apoptosis was partially mediated by nuclear factor of activated T cells (NFAT3) signaling and partially by **Akt/ protein kinase B** (**PKB**) signaling.
Although calcineurin activation protected myocytes from apoptosis, inhibition of calcineurin with cyclosporine was not sufficient to induce TUNEL labeling in Gq alpha-transgenic mice or in cultured cardiomyocytes. Collectively, these data identify a calcineurin-dependent mouse model of dilated heart failure that is independent of apoptosis.

L5 ANSWER 4 OF 10 SCISEARCH COPYRIGHT 2000 ISI (R)
ACCESSION NUMBER: 2000:272556 SCISEARCH
THE GENUINE ARTICLE: 300UY
TITLE: Cytokines and their receptors in cardiovascular diseases - role of gp130 signalling pathway in cardiac myocyte growth and maintenance
AUTHOR: YamauchiTakihara K (Reprint); Kishimoto T
CORPORATE SOURCE: OSAKA UNIV, SCH MED, DEPT MOL MED, 2-2 YAMADAOKA, SUITA, OSAKA 5650871, JAPAN (Reprint)
COUNTRY OF AUTHOR: JAPAN
SOURCE: INTERNATIONAL JOURNAL OF EXPERIMENTAL PATHOLOGY, (FEB 2000 ) Vol. 81, No. 1, pp. 1-16.
Publisher: BLACKWELL SCIENCE LTD, P O BOX 88, OSNEY MEAD, OXFORD OX2 0NE, OXON, ENGLAND.
ISSN: 0959-9673.
DOCUMENT TYPE: General Review; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 127
*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB Interleukin (IL)-6-related cytokines share gp130 as the signal-transducing protein. Cardiac myocytes produce various kinds of cytokines including IL-6 and cardiotrophin-1. Activation of gp130 transduces hypertrophic and cytoprotective signals in cardiac myocytes via JAK/STAT, MAP kinase and PI-3 kinase pathways. Besides various well-established mechanisms by which cardiac growth and myocardial remodeling are regulated, gp130 signalling may be a newly discovered mechanism that regulates these events in association with cytoprotective effect in myocardial diseases.

L5 ANSWER 5 OF 10 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999420723 EMBASE
TITLE: Adenoviral gene transfer of activated phosphatidylinositol 3'-kinase and **Akt** inhibits apoptosis of hypoxic cardiomyocytes in vitro.
AUTHOR: Matsui T.; Li L.; Del Monte F.; Fukui Y.; Franke T.F.; Hajjar R.J.; Rosenzweig A.
CORPORATE SOURCE: Dr. A. Rosenzweig, Cardiovascular Research Center,

MGH-East, 149 13th St, Charlestown, MA 02129, United States. rosenzweig@helix.mgh.harvard.edu
SOURCE: Circulation, (7 Dec 1999) 100/23 (2373-2379). Refs: 20 ISSN: 0009-7322 CODEN: CIRCAZ
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
018 Cardiovascular Diseases and Cardiovascular Surgery
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Background - The intracellular signaling pathways that control cardiomyocyte apoptosis have not been fully defined. Because insulin-like growth factor-1 (IGF-1) prevents cardiomyocyte apoptosis, we examined the role of its downstream signaling molecules in an in vitro model of hypoxia- induced cardiomyocyte apoptosis. Methods and Results - Treatment of rat neonatal cardiomyocytes with IGF-1 increased activity of both phosphatidylinositol 3' (PI 3)-kinase and its downstream target, **Akt** (also known as **protein kinase B** or **PKB**). Cardiomyocytes were subjected to hypoxia for 24 hours, and apoptosis was assessed by DNA laddering, TUNEL staining, and ELISA for histone-associated DNA fragments. IGF-1 treatment (100 nmol/L) reduced cardiomyocyte apoptosis, and this effect was inhibited by simultaneous treatment with a PI 3-kinase inhibitor. Cardiomyocytes were infected with either a control adenovirus (Ad.EGFP) or adenoviruses carrying constitutively active forms of PI 3-kinase (Ad.BD110) or **Akt** (Ad.myr-**Akt**-HA). Ad.BD110 significantly inhibited apoptosis of hypoxic cardiomyocytes compared with Ad:EGFP (61.0.+-.4.6% less DNA fragmentation than in Ad.EGFP-infected cells, P<0.0001). Ad.myr-**Akt**-HA even more dramatically inhibited apoptosis of hypoxic cardiomyocytes (90.9.+-.1.4% less DNA fragmentation than in controls, P<0.0001). Conclusions - IGF-1 activates PI 3-kinase and **Akt** in cardiomyocytes. Activated PI 3-kinase and **Akt** are each sufficient to protect hypoxic cardiomyocytes against apoptosis in vitro. Adenoviral gene transfer provides a useful tool for investigating the role of these signaling pathways in cardiomyocyte apoptosis.

L5 ANSWER 6 OF 10 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999395142 EMBASE
TITLE: Cardiac myocyte apoptosis.
AUTHOR: Cook S.A.; Poole-Wilson P.A.
CORPORATE SOURCE: Dr. S.A. Cook, NHLI Division - Cardiac Medicine, Imperial College of Medicine, Dovehouse Street, London SW3 6LY, United Kingdom
SOURCE: European Heart Journal, (1999) 20/22 (1619-1629). Refs: 90 ISSN: 0195-668X CODEN: EHJODF
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
018 Cardiovascular Diseases and Cardiovascular Surgery
022 Human Genetics
029 Clinical Biochemistry
LANGUAGE: English

L5 ANSWER 7 OF 10 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2000069026 MEDLINE

DOCUMENT NUMBER: 20069026
TITLE: Desensitization and resensitization of beta 1- and putative beta 4-adrenoceptor mediated responses occur in parallel in a rat model of cardiac failure.
AUTHOR: Kompa A R; Summers R J
CORPORATE SOURCE: Department of Pharmacology, Monash University, Wellington Road, Clayton, Victoria, 3168, Australia.
SOURCE: BRITISH JOURNAL OF PHARMACOLOGY, (1999 Dec) 128 (7) 1399-406.
Journal code: B00. ISSN: 0007-1188.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY WEEK: 20000401

AB 1. Cardiostimulant effects of the non-conventional partial agonist, CGP 12177A, are mediated by a receptor distinct from the beta3-adrenoceptor and termed the putative beta4-adrenoceptor. Using a rat model of cardiac failure, induced by myocardial **infarction** (MI), we compared the desensitization and resensitization of responses to CGP 12177A with those to isoprenaline and RO 363 in left (LA) and right atria (RA). We also examined the ability of beta-adrenoceptor antagonists to block responses to CGP 12177A. 2. MI reduced the maximum inotropic response to isoprenaline by 48% (sham 4.1+/-0.6 mN, n=10; MI 2.1+/-0.4 mN, n=8, P<0.02), RO 363 by 61% (sham 4.2+/-0.5 mN, n=10; MI 1.8+/-0.3 mN, n=8, P<0.005) and CGP 12177A by 49% (sham 1.4+/-0.1 mN, n=5; MI 0.7+/-0.2 mN, n=7, P<0.05) in electrically stimulated LA. MI also reduced the sensitivity to isoprenaline (pEC50: sham 8.79+/-0.08, n=10; MI 8.30+/-0.10, n=8; P=0.001) and RO 363 (pEC50: sham 8.69+/-0.07, n=10; MI 8.33+/-0.10, n=8; P<0.01). The maximum chronotropic responses to isoprenaline, RO 363 and CGP 12177A in RA were unaffected. 3. Pertussis toxin treatment (10 &mgr;g kg-1, i.p.) restored the maximum inotropic response and sensitivity to isoprenaline (sham 3.5+/-0.5 mN, n=9; MI 3.2+/-0.6 mN, n=11, P=0.702) and CGP 12177A (sham 1.6+/-0.3 mN, n=6; MI 1.9+/-0.4 mN, n=7, P=0.537) in MI animals to levels similar to those in the sham group. 4. CGP 20712A (**pKB**: LA 6.7+/-0.2, n=6; RA 7.1+/-0.1, n=4), ICI 118,551 (**pKB**: LA 6.4+/-0.1, n=5; RA 6.3+/-0.1, n=6), propranolol (**pKB**: LA 6.6+/-0.1, n=5; RA 6.8+/-0.1, n=6) and bupranolol (**pKB**: LA 7.2+/-0.1, n=6; RA 7.7+/-0.1, n=8), showed moderate affinity for the putative beta4-adrenoceptor. 5. Desensitization after MI and resensitization (after pertussis toxin treatment) to isoprenaline and CGP 12177A therefore occur in parallel, suggesting that the beta1- and putative beta4-adrenoceptor use the same signalling pathway. Antagonist affinity studies confirmed that drugs acting at beta1-adrenoceptors also interact with putative beta4-adrenoceptors with approximately 100 times lower affinity. We suggest that CGP 12177A produces its cardiac effects by interacting with a low affinity state of the beta1-adrenoceptor.

L5 ANSWER 8 OF 10 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 1999458099 MEDLINE
DOCUMENT NUMBER: 99458099
TITLE: Immunoreactive **Akt**, PI3-K and ERK protein kinase expression in ischemic rat brain.

AUTHOR: Kitagawa H; Warita H; Sasaki C; Zhang W R; Sakai K; Shiro Y; Mitsumoto Y; Mori T; Abe K
CORPORATE SOURCE: Department of Neurology, Okayama University Medical School, Japan.
SOURCE: NEUROSCIENCE LETTERS, (1999 Oct 15) 274 (1) 45-8. Journal code: N7N. ISSN: 0304-3940.
PUB. COUNTRY: Ireland
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY WEEK: 20000402

AB In order to clarify the role of protein kinases in ischemic brain injury, the spatiotemporal expression of immunoreactive serine-threonine kinase **Akt**, phosphatidylinositol 3-kinase (PI3-K) and extracellular signal-regulated kinase (ERK) were examined at 3, 8, or 24 h after permanent middle cerebral artery occlusion (MCAO) in rats. Weak staining for these protein kinases was found in both cortical and caudate neurons in sham controls. The staining for **Akt**-1 and PI3-K was increased at 3-8 h in the ischemic penumbral region and declined at 24 h. A slight induction of these kinases was observed in the ischemic core region. Robust expression of ERK was noted at 3-8 h in most neurons in the area of ischemia. At 24 h, ERK continued to be expressed in the ischemic penumbra, but decreased in the ischemic core. These findings suggest that the signaling for **Akt** and PI3-K are different from the ERK dependent signal transduction during ischemic brain injury.

L5 ANSWER 9 OF 10 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 2000:32325 BIOSIS
DOCUMENT NUMBER: PREV200000032325
TITLE: **Akt** mediates IGF-1 cytoprotection of cardiomyocytes in vitro and protects against ischemia-reperfusion injury in mouse heart.
AUTHOR(S): Fujio, Yasushi (1); Kitsis, Richard N.; Walsh, Kenneth
CORPORATE SOURCE: (1) St Elizabeth's Med Ctr, Boston, MA USA
SOURCE: Circulation, (Nov. 2, 1999) Vol. 110, No. 18 SUPPL., pp. I.9.
Meeting Info.: 72nd Scientific Sessions of the American Heart Association Atlanta, Georgia, USA November 7-10, 1999.
ISSN: 0009-7322.
DOCUMENT TYPE: Conference
LANGUAGE: English

L5 ANSWER 10 OF 10 MEDLINE
ACCESSION NUMBER: 80232137 MEDLINE
DOCUMENT NUMBER: 80232137
TITLE: [Myocardial infarct--last act in a drama]. Myokardinfarkt--letzter **Akt** eines Dramas.
AUTHOR: Stossel J P
SOURCE: MEDIZINISCHE KLINIK, (1980 May 9) 75 (10) 347. Journal code: M4E. ISSN: 0025-8458.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: German
FILE SEGMENT: Priority Journals

ENTRY MONTH: 198011

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(FILE 'HOME' ENTERED AT 09:44:20 ON 27 NOV 2000)

FILE 'MEDLINE, CANCERLIT, BIOSIS, EMBASE, SCISEARCH' ENTERED AT 09:44:28 ON 27 NOV 2000

L1 6893 S AKT OR PROTEIN KINASE B OR PKB
L2 3320 S WALSH-K?/AU
L3 55 S L1 AND L2
L4 17 S L1 AND INFARCTION
L5 10 DUP REM L4 (7 DUPLICATES REMOVED)

=> dup rem l3

PROCESSING COMPLETED FOR L3
L6 22 DUP REM L3 (33 DUPLICATES REMOVED)

=> s l6 and py<1999

2 FILES SEARCHED...
3 FILES SEARCHED...
L7 3 L6 AND PY<1999

=> d ibib abs 1-3

L7 ANSWER 1 OF 3 MEDLINE
ACCESSION NUMBER: 96032568 MEDLINE
DOCUMENT NUMBER: 96032568
TITLE: Cloning, chromosomal localization and expression analysis of the mouse Akt2 oncogene.
AUTHOR: Altomare D A; Guo K; Cheng J Q; Sonoda G; **Walsh K**; Testa J R
CORPORATE SOURCE: Department of Medical Oncology, Fox Chase Cancer Center, Philadelphia, Pennsylvania 19111, USA.
CONTRACT NUMBER: CA 09035 (NCI)
CA-06927 (NCI)
SOURCE: ONCOGENE, **(1995 Sep 21)** 11 (6) 1055-60.
Journal code: ONC. ISSN: 0950-9232.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Cancer Journals; Priority Journals
OTHER SOURCE: GENBANK-U22445
ENTRY MONTH: 199601
AB We isolated mouse cDNA clones containing the entire coding region of the putative oncogene Akt2. Sequence analysis revealed that, like its human homolog, Akt2 encodes a protein-serine/threonine kinase containing a pleckstrin homology domain at its amino terminus. Fluorescence in situ hybridization of the mouse cDNA to rodent metaphase spreads demonstrated that the Akt2 gene maps to mouse chromosome band 7B1 and rat chromosome 1q22. Expression levels of mouse Akt2 mRNA and Akt2 protein varied among tissues, with the highest levels in skeletal muscle. Akt2 expression was low in a multipotent fibroblast cell line, but it was upregulated when these cells were transformed with Myod and induced to differentiate into

myocytes. These data demonstrate that Akt2 expression is activated during cellular differentiation and suggest that it functions in the signaling pathways of some adult tissues.

L7 ANSWER 2 OF 3 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1999:524212 BIOSIS
DOCUMENT NUMBER: PREV199900524212
TITLE: **Akt** mediates the cell survival effects of vascular endothelial growth factor.
AUTHOR(S): Fujio, Yasushi; Mano, Toshiaki; Takahashi, Tomono (1); **Walsh, Kenneth**
CORPORATE SOURCE: (1) St. Elizabeth's Med. Cent., Boston, MA USA
SOURCE: Circulation, (**Oct. 27, 1998**) Vol. 98, No. 17 SUPPL., pp. I463.
Meeting Info.: 71st Scientific Sessions of the American Heart Association Dallas, Texas, USA November 8-11, 1998 The American Heart Association
. ISSN: 0009-7322.
DOCUMENT TYPE: Conference
LANGUAGE: English

L7 ANSWER 3 OF 3 SCISEARCH COPYRIGHT 2000 ISI (R)
ACCESSION NUMBER: 1998:885070 SCISEARCH
THE GENUINE ARTICLE: 131UV
TITLE: **Akt** mediates the cell survival effects of vascular endothelial growth factor.
AUTHOR: Fujio Y (Reprint); Mano T; **Walsh K**
CORPORATE SOURCE: ST ELIZABETHS MED CTR, BOSTON, MA
COUNTRY OF AUTHOR: USA
SOURCE: CIRCULATION, (**27 OCT 1998**) Vol. 98, No. 17, Supp. [S], pp. 2436-2436.
Publisher: WILLIAMS & WILKINS, 351 WEST CAMDEN ST, BALTIMORE, MD 21201-2436.
ISSN: 0009-7322.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: English
REFERENCE COUNT: 0

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(FILE 'HOME' ENTERED AT 09:44:20 ON 27 NOV 2000)

FILE 'MEDLINE, CANCERLIT, BIOSIS, EMBASE, SCISEARCH' ENTERED AT 09:44:28 ON 27 NOV 2000
L1 6893 S AKT OR PROTEIN KINASE B OR PKB
L2 3320 S WALSH-K?/AU
L3 55 S L1 AND L2
L4 17 S L1 AND INFARCTION
L5 10 DUP REM L4 (7 DUPLICATES REMOVED)
L6 22 DUP REM L3 (33 DUPLICATES REMOVED)
L7 3 S L6 AND PY<1999

=> s l1 and py<1998

2 FILES SEARCHED...
3 FILES SEARCHED...

L8 1681 L1 AND PY<1998

=> s l8 and vivo

L9 130 L8 AND VIVO

=> s l9 and (cardio? or myo?)

L10 13 L9 AND (CARDIO? OR MYO?)

=> dup rem l10

PROCESSING COMPLETED FOR L10
L11 8 DUP REM L10 (5 DUPLICATES REMOVED)

=> d ibib abs 1-8

L11 ANSWER 1 OF 8 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1998:52465 BIOSIS
DOCUMENT NUMBER: PREV199800052465
TITLE: Pharmacologic profiles of KRH-594, a novel nonpeptide angiotensin II-receptor antagonist.
AUTHOR(S): Tamura, Koichi (1); Okuhira, Masayasu; Amano, Hirotaka; Inokuma, Ken-Ichi; Hirata, Terukage; Mikoshiba, Imao; Hashimoto, Ken
CORPORATE SOURCE: (1) Inst. Med. Res., Wakunaga Pharm. Co. Ltd., 1624 Shimokotachi, Takata-gun, Hiroshima 739-11 Japan
SOURCE: Journal of Cardiovascular Pharmacology, (**Nov., 1997**) Vol. 30, No. 5, pp. 607-615.
ISSN: 0160-2446.
DOCUMENT TYPE: Article
LANGUAGE: English
AB We studied pharmacologic profiles of KRH-594, dipotassium (Z)-2-((5-ethyl-3-(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl-1,3,4-thiadiazolin-2-ylidene)aminocarbonyl)-1-cyclopentenecarboxylate, a novel angiotensin II (AII)-receptor antagonist. KRH-594 potently displaced specific binding of (125I)-AII from AT1 receptor with a Ki of 0.39 nM in rat liver membranes, but not from AT2 receptor in bovine cerebellar membranes (Ki > 10 muM). KRH-594 exhibited no affinity for 21 other receptors and two enzymes (50% inhibitory concentration (IC50) > 10 muM, demonstrating its high specificity toward AT1 receptors. In isolated rabbit aorta, KRH-594 caused nonparallel shifts to the right of the dose-response curve to AII and decreased the maximal response with a **pKB** of 10.4. We evaluated the in **vivo** efficacy and the duration of action in freely moving rats under nonfasting conditions. In normotensive rats, orally administered KRH-594 inhibited AII-induced pressor responses with a 50% inhibitory dose (ID50) of 0.39 mg/kg. In spontaneously hypertensive rats (SHRs), both KRH-594 (1 mg/kg p.o.) and losartan (10 mg/kg p.o.) exerted similar blood pressure-reducing effects, and their effects were still significant at 24 h after drug administration. We concluded that KRH-594 is a specific and efficacious AT1 antagonist that may find its use in the treatment of human hypertension.

L11 ANSWER 2 OF 8 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 97133284 MEDLINE
DOCUMENT NUMBER: 97133284
TITLE: Mechanism of activation of **protein kinase**

**B** by insulin and IGF-1.

AUTHOR: Alessi D R; Andjelkovic M; Caudwell B; Cron P; Morrice N; Cohen P; Hemmings B A

CORPORATE SOURCE: MRC Protein Phosphorylation Unit, Department of Biochemistry, University of Dundee, UK.

SOURCE: EMBO JOURNAL, **(1996 Dec 2)** 15 (23) 6541-51. Journal code: EMB. ISSN: 0261-4189.

PUB. COUNTRY: ENGLAND: United Kingdom Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199704

AB Insulin activated endogenous **protein kinase B** alpha (also known as RAC/**Akt** kinase) activity 12-fold in L6 **myotubes**, while after transfection into 293 cells PKBalpha was activated 20- and 50-fold in response to insulin and IGF-1 respectively. In both cells, the activation of PKBalpha was accompanied by its phosphorylation at Thr308 and Ser473 and, like activation, phosphorylation of both of these residues was prevented by the phosphatidylinositol 3-kinase inhibitor wortmannin. Thr308 and/or Ser473 were mutated to Ala or Asp and activities of mutant PKBalpha molecules were analysed after transfection into 293 cells. The activity of wild-type and mutant PKBalpha was also measured in vitro after stoichiometric phosphorylation of Ser473 by MAPKAP kinase-2. These experiments demonstrated that activation of PKBalpha by insulin or insulin-like growth factor-1 (IGF-1) results from phosphorylation of both Thr308 and Ser473, that phosphorylation of both residues is critical to generate a high level of PKBalpha activity and that the phosphorylation of Thr308 in **vivo** is not dependent on phosphorylation of Ser473 or vice versa. We propose a model whereby PKBalpha becomes phosphorylated and activated in insulin/IGF-1-stimulated cells by an upstream kinase(s).

L11 ANSWER 3 OF 8 BIOSIS COPYRIGHT 2000 BIOSIS

ACCESSION NUMBER: 1996:312953 BIOSIS

DOCUMENT NUMBER: PREV199699035309

TITLE: Interstitial adenosine and function in rat heart in **vivo**: Effects of adrenaline and 8-cyclopentyl-1,3-dimethylxanthine.

AUTHOR(S): Headrick, John P.

CORPORATE SOURCE: Dep. Physiol. Pharmacol., Sch. Mol. Sci., James Cook Univ. North Qld., Townsville, Qld. 4811 Australia

SOURCE: Clinical and Experimental Pharmacology and Physiology, (1996) Vol. 23, No. 5, pp. 386-394. ISSN: 0305-1870.

DOCUMENT TYPE: Article

LANGUAGE: English

AB 1. Left ventricular interstitial adenosine and cardiac function were studied in open chest rats during adrenaline stimulation and P-1-purinoceptor antagonism with 8-cyclopentyl-1,3-dimethylxanthine (8-CPT). 2. Cardiac microdialysate adenosine concentration was 0.10 +- 0.01 mu-mol/L (n = 24) under basal conditions, giving an estimated interstitial adenosine concentration of 0.27 mu-mol/L. Stimulation with 3.2 and 8.0 mu-g/kg per min adrenaline increased the rate-pressure product (heart rate X systolic blood pressure) by 72 and 157%, respectively, and increased dialysate adenosine to 0.26 +- 0.04 and 0.65 +- 0.11 mu-mol/L (n

= 12), respectively (interstitial concentrations of approximately 0.70 and 1.76 mu-mol/L). 3. Treatment with 60 mu-g/kg per min 8-CPT did not alter basal adenosine concentrations, but potentiated elevations in dialysate adenosine during infusion of 3.2 and 8.0 mu-g/kg per min adrenaline to 0.54 +- 0.10 and 1.30 +- 0.22 mu-mol/L, respectively (n = 12). Basal function and the response to 8.0 mu-g/kg per min adrenaline were unaltered by 8-CPT, whereas elevations in heart rate and rate-pressure product during stimulation with 3.2 mu-g/kg per min adrenaline were enhanced by 8-CPT (by up to 30%). 4. Studies in isolated hearts confirmed the inhibitory potency of 8-CPT at A-1 vs A-2 P-i-purinoceptors (e.g. **pKB** of 7.7 +- 0.2 and 6.4 +- 0.1 for 5'-N-ethyl carboxamidoadenosine-mediated bradycardia and vasodilatation, respectively; n = 6). Studies in intact animals verified effective A-1 blockade by 60 mu-g/kg per min 8-CPT, but also revealed some inhibition of A-2-mediated responses. 5. In conclusion, the data show that cardiac interstitial adenosine levels exist within a physiologically active range in **vivo** and increase dose-dependently during graded adrenaline stimulation. Adenosine receptor antagonism enhances elevations in interstitial adenosine and modifies functional responses to moderate, but not high, doses of adrenaline. Whether 8-CPT-dependent elevations in interstitial adenosine are due to A-2 inhibition vs inhibition of A-2-mediated vasodilatation requires further investigation.

L11 ANSWER 4 OF 8 MEDLINE
ACCESSION NUMBER: 96342435 MEDLINE
DOCUMENT NUMBER: 96342435
TITLE: Blockade of human and porcine **myocardial** 5-HT4 receptors by SB 203186.
AUTHOR: Parker S G; Taylor E M; Hamburger S A; Vimal M; Kaumann A J
CORPORATE SOURCE: Smith Kline Beechman Pharmaceuticals, Welwyn, UK.
SOURCE: NAUNYN-SCHMIEDEBERGS ARCHIVES OF PHARMACOLOGY, **(1995 Dec)** 353 (1) 28-35.
Journal code: NTQ. ISSN: 0028-1298.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199701
ENTRY WEEK: 19970104

AB We investigated the blockade of the positive inotropic effects of 5-hydroxytryptamine (5-HT) by SB 203 186 (piperidinoethyl-indole-3-carboxylate hydrochloride) and its affinity for 5-HT4 receptors of human right atrium and piglet left atrium. We also compared the blocking effects of SB 203 186 against 5-HT-evoked tachycardia in anaesthetised adult Yucatan minipigs as well as new-born Camborough piglets. SB 203 186 caused competitive antagonism of the positive inotropic effects of 5-HT in electrically paced atrial preparations of man (**pKB** = 8.9) and piglet (**pKB** = 8.5) at concentrations (up to 0.3 micromol/l) which were devoid of depressant or stimulant effects. The affinity of SB 203 186 for atrial 5-HT4 receptors was 30-160 times higher than that of tropisetron. 5-HT caused tachycardia with similar potency and efficacy in Yucatan minipigs and new-born Camborough piglets. SB 203 186 (0.1-3 mg/kg,

i.v.) surmountably antagonised 5-HT-evoked tachycardia in anaesthetised Yucatan minipigs or new-born Camborough piglets with similar potency. The blocking potency of SB 203 186 in Yucatan minipigs was 17 times higher than that of tropisetron. Intraduodenally administered SB 203 186 (0.3-3 mg/kg) to new-born Camborough piglets produced blockade of 5-HT-evoked tachycardia which was maximal after 20 min and lasted for more than 3 h with 0.3 mg/kg. The antagonism produced by the SB 203 186 administration in new-born Camborough piglets was dose-related and threefold greater through the intravenous route than through the intraduodenal route. We conclude that SB 203 186 is an antagonist with nanomolar affinity for both human and porcine atrial 5-HT4 receptor. The in **vivo** results demonstrate that the sinoatrial 5-HT4 receptors function is similar in new-born Camborough piglets and adult Yucatan minipigs. Both porcine breeds are valid models for human atrial 5-HT4 receptors as demonstrated with the antagonist SB 203 186.

L11 ANSWER 5 OF 8 MEDLINE
ACCESSION NUMBER: 94061396 MEDLINE
DOCUMENT NUMBER: 94061396
TITLE: Pharmacological profile of valsartan: a potent, orally active, nonpeptide antagonist of the angiotensin II AT1-receptor subtype.
AUTHOR: Criscione L; de Gasparo M; Buhlmayer P; Whitebread S; Ramjoue H P; Wood J
CORPORATE SOURCE: Cardiovascular Research Department, CIBA-GEIGY Limited, Basel, Switzerland.
SOURCE: BRITISH JOURNAL OF PHARMACOLOGY, **(1993 Oct)** 110 (2) 761-71.
Journal code: B00. ISSN: 0007-1188.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199403

AB 1. The pharmacological profile of valsartan, (S)-N-valeryl-N-([2'-(1H-tetrazol-5-yl)biphenyl-4-yl]-methyl)-vali ne, a potent, highly selective, and orally active antagonist at the angiotensin II (AII) AT1-receptor, was studied in vitro and in **vivo**. 2. Valsartan competed with [125I]-AII at its specific binding sites in rat aortic smooth muscle cell membranes (AT1-receptor subtype) with a Ki of 2.38 nM, but was about 30,000 times less active in human **myometrial** membranes (AT2-receptor subtype). 3. In rabbit aortic rings incubated for 5 min with valsartan, at concentrations of 2, 20 and 200 nM, the concentration-response curve of AII was displaced to the right and the maximum response was reduced by 33%, 36% and 40%, respectively. Prolongation of the incubation time with valsartan to 1 h or 3 h, further reduced the maximum response by 48% or 59% (after 20 nM) and by 59% or 60% (after 200 nM) respectively. After 3 h incubation an apparent **pKb** value of 9.26 was calculated. Contractions induced by noradrenaline, 5-hydroxytryptamine, or potassium chloride were not affected by valsartan.

No agonistic effects were observed in the rabbit aorta at concentrations of valsartan up to 2 microM. 4. In bovine adrenal glomerulosa, valsartan inhibited AII-stimulated aldosterone release without affecting the maximum response (pA2 8.4). 5. In the pithed rat, oral administration of valsartan

(10 mg kg-1) shifted the AII-induced pressor response curves to the right, without affecting responses induced by the electrical stimulation of the sympathetic outflow or by noradrenaline. Animals treated with valsartan 24 h before pithing also showed significant inhibition of the response to AII. 6. In conscious, two-kidney, one-clip renal hypertensive rats (2K1C), valsartan decreased blood pressure in a dose-dependent manner after single i.v. or oral administration. The respective ED30 values were 0.06 mg kg-1 (i.v.) and 1.4 mg kg-1 (p.o.). The antihypertensive effect lasted for at least 24 h after either route of administration. After repeated oral administration for 4 days (3 and 10 mg kg-1 daily), in 2K1C renal hypertensive rats, systolic blood pressure was consistently decreased, but heart rate was not significantly affected. 7. In conscious, normotensive, sodium-depleted marmosets, valsartan decreased mean arterial pressure, measured by telemetry, after oral doses of 1-30 mg kg-1. The hypotensive effect persisted up to 12 h after 3 and 10 mg kg-1 and up to 24 h after 30 mg kg-1.(ABSTRACT TRUNCATED AT 400 WORDS)

L11 ANSWER 6 OF 8 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 91374449 MEDLINE
DOCUMENT NUMBER: 91374449
TITLE: (Phenylmethoxy)phenyl derivatives of omega-oxo- and omega-tetrazolylalkanoic acids and related tetrazoles. Synthesis and evaluation as leukotriene D4 receptor antagonists.
AUTHOR: Dillard R D; Hahn R A; McCullough D; Carr F P; Rinkema L E; Roman C R; Fleisch J H
CORPORATE SOURCE: Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46285..
SOURCE: JOURNAL OF MEDICINAL CHEMISTRY, **(1991 Sep)** 34 (9) 2768-78.
Journal code: J0F. ISSN: 0022-2623.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199112

AB Two series of (phenylmethoxy)phenyl compounds derived from the structure of LY163443 were synthesized and evaluated as leukotriene D4 receptor antagonists. In the omega-[(phenylmethoxy)phenyl]-omega-oxoalkanoic acid series, 5-[4-[(4-acetyl-2-ethyl-3-hydroxyphenyl)methoxy]phenyl]-3,3-dimethyl-5- oxopentanoic acid (8) was the most potent antagonist of LTD4-induced contractions of guinea pig ileum (**pKB** of 7.60) and LTD4 pressor response in pithed rats (ED50 of 1.4 mg/kg iv). Replacing the carboxylic acid function with 5-tetrazole gave slightly more potent compounds. In the omega-[5-[[(phenylmethoxy)phenyl]alkyl] tetrazolyl]alkanoic acid series, replacing the carboxylic acid with 5-tetrazole gave compounds that were equally effective in the guinea pig ileum but more potent in **vivo** against the LTD4 pressor response in rat. The **pKB** value in the guinea pig ileum for 1-[2-hydroxy-3-propyl-4-[[4-[[2-[3-(1H-tetrazol-5-yl)propyl]-2H-tetrazol-

5-yl]methyl ] phenoxy]methyl]phenyl]ethanone (25) was 7.87 and the ED50 for antagonism of the LTD4 pressor response was 4.0 mg/kg iv. The sodium salts of 8 (9) and 25 (26) given by the iv route of administration antagonized LTD4-induced **cardiovascular** alterations in anesthetized rat and LTD4-induced bronchoconstriction in guinea pig in a dose-dependent manner. Oral activity was also demonstrated against the LTD4-induced bronchoconstriction in guinea pig.

L11 ANSWER 7 OF 8 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1989:3871 BIOSIS
DOCUMENT NUMBER: BA87:3871
TITLE: MOLECULAR MECHANISM OF THE INHIBITORY EFFECTS OF ISOQUINOLINESULFONAMIDES ON PROTEIN KINASES.
AUTHOR(S): HAGIWARA M
CORPORATE SOURCE: DEP. PHARMACOL., NAGOYA UNIV. SCH. MED., SHOWA-KU, NAGOYA 466, JPN.
SOURCE: MIE MED J, (1988) 38 (2), 137-154.
CODEN: MMJJAI. ISSN: 0026-3532.
FILE SEGMENT: BA; OLD
LANGUAGE: English

AB Molecular properties of MLC-kinase, protein kinase C, and cAMP-dependent protein kinase were analysed using selective inhibitors of isoquinolinesulfonamide derivatives. These protein kinases were potently inhibited by 1-(8-chloro-5-isoquinolinesulfonyl) piperazine (HA-156) and its derivatives. Kinetic analysis indicated that HA-156 inhibited both enzymes competitively with respect to ATP, and ki values of HA-156 for MLC-kinase and protein kinase C were 7.3 and 7.2 .mu.M, respectively. To clarify molecular mechanisms of the isoquinolinesulfonamides to inhibit the Ca2+-dependent protein kinases, the structure-activity relationships of HA-156 and its derivatives were examined. The dechlorinated analogues, HA-100 and HA-142, markedly decreased the affinity for MLC-kinase, suggesting that the inhibitory effect of isoquinolinesulfonamide derivatives depends upon the hydrophobicity of the compounds. There is a good correlation between MLC-kinase inhibition and hydrophobicity determined by reverse phase chromatography. In contrast, HA-140 and HA-142 showed weak inhibition of protein kinase C, suggesting that the electron density of the nitrogen in the isoquinoline ring of the compounds correlates with the potency to inhibit protein kinase C activity. When the piperazine ring was replaced by the methylaminoethyl chain, the compound, named H-8, specifically inhibited cyclic nucleotide dependent protein kinases and did not affect Ca2+-dependent enzymes. The interaction of H-8 with the catalytic subunit of cAMP-dependent protein kinase was studied, using various affinity labeling reagents of the ATP binding site of the purified protein kinase catalytic subunit and the gelpermeation binding assay. The data showed that H-8 specifically binds to the ATP binding site of the catalytic subunit with a binding ratio of 1:1 and that H-8 has unique features which differ from the ATP analogues, in the following points: a) H-8, among other protein kinases or ATP utilizing enzymes, specifically inhibits cyclic nucleotide-dependent **protein kinase**; **b**) the binding constant (Km) of H-8 to the enzyme is much lower than that of ATP; c) the binding of H-8 to the enzyme is independent of magnesium ion; d) the binding subsite of H-8 at the active site of the enzyme slightly differs from that of ATP. These isoquinolinesulfonamide derivatives should prove to be useful tools for distinguishing the role of each protein kinase, in **vivo**.

L11 ANSWER 8 OF 8 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1981:241175 BIOSIS
DOCUMENT NUMBER: BA72:26159
TITLE: AN IN-VITRO QUANTITATIVE ANALYSIS OF THE ALPHA ADRENOCEPTOR
PARTIAL AGONIST ACTIVITY OF DOBUTAMINE AND ITS RELEVANCE TO
INOTROPIC SELECTIVITY.
AUTHOR(S): KENAKIN T P
CORPORATE SOURCE: DEP. PHARMACOL., BURROUGHS WELLCOME CO., 3030 CORNWALLIS RD., RES. TRIANGLE PARK, NC 27709.
SOURCE: J PHARMACOL EXP THER, (1981) 216 (2), 210-219.
CODEN: JPETAB. ISSN: 0022-3565.
FILE SEGMENT: BA; OLD
LANGUAGE: English

AB In rat anococcygeus muscle, dobutamine [D3] produced concentration-related submaximal contractions which were antagonized competitively by phentolamine [PHEN] (**pKB** [pK for .beta.-receptors] = 8.3) and D antagonized norepinephrine[NE]-induced contractions in a competitive manner with an Kd for the .alpha.-adrenoceptor of 20 nM (**pKB** = 7.7). Therefore, D satisfied criteria for a partial agonist of .alpha.-adrenoceptors having an affinity for .alpha.-adrenoceptors 25 times that of NE (pKA [pK for .alpha.-receptor] = 6.3) in this tissue. An estimate of the relative efficacy of D showed 1/40 the efficacy of NE at the .alpha.-adrenoceptors. D contracted rabbit aorta and produced concentration-related relaxations at 1000 times greater concentrations after alkylation of .alpha.-adrenoceptors by phenoxybenzamine. In noncontracted canine saphenous vein, D had no visible agonist activity but did produce contractions after propranolol [PRO]. In partially contracted saphenous vein, D produced a small contraction which was converted to a PRO-sensitive relaxation of tone after PHEN. D was a full .beta.-adrenoceptor agonist in guinea-pig trachea under spontaneous tone but a partial agonist after strong contraction by bethanechol. This allowed measurement of the **pKB** of D at .beta.-adrenoceptors ( **pKB** = 5.35) and estimation of efficacy at .beta.-adrenoceptors relative to isoproterenol [ISO] (eD/eISO = 1/20). No evidence for .beta.-adrenoceptor selectivity was found in studies of potency ratios and relative efficacy using ISO for comparison. D showed a slight (2-fold) selectivity for inotropy in vitro when compared to ISO in guinea-pig right and left atria. This selectivity was removed by PHEN suggesting a cardiac .alpha.-like adrenoceptor effect; this finding was confirmed in PRO-treated guinea-pig left atria. These results are discussed in terms of the in **vivo** effects of D and its use as a tool for classification of .beta.-adrenoceptors, particularly the putative presynaptic .beta.-adrenoceptor.

=> d his

(FILE 'HOME' ENTERED AT 09:44:20 ON 27 NOV 2000)

FILE 'MEDLINE, CANCERLIT, BIOSIS, EMBASE, SCISEARCH' ENTERED AT 09:44:28

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     ON 27 NOV 2000
L1          6893 S AKT OR PROTEIN KINASE B OR PKB
L2          3320 S WALSH-K?/AU
L3            55 S L1 AND L2
L4            17 S L1 AND INFARCTION
L5            10 DUP REM L4 (7 DUPLICATES REMOVED)
L6            22 DUP REM L3 (33 DUPLICATES REMOVED)
L7             3 S L6 AND PY<1999
L8          1681 S L1 AND PY<1998
L9           130 S L8 AND VIVO
L10           13 S L9 AND (CARDIO? OR MYO?)
L11            8 DUP REM L10 (5 DUPLICATES REMOVED)

=> s l9 not pkb

L12          38 L9 NOT PKB

=> dup rem l12

PROCESSING COMPLETED FOR L12
L13           11 DUP REM L12 (27 DUPLICATES REMOVED)

=> d ibib abs 1-11


L13  ANSWER 1 OF 11  MEDLINE                                  DUPLICATE 1
ACCESSION NUMBER:    97190268      MEDLINE
DOCUMENT NUMBER:     97190268
TITLE:               A novel, rapid, and highly sensitive mass assay for
                     phosphatidylinositol 3,4,5-trisphosphate (PtdIns(3,4,5)P3)
                     and its application to measure insulin-stimulated
                     PtdIns(3,4,5)P3 production in rat skeletal muscle in
                     vivo.
AUTHOR:              van der Kaay J; Batty I H; Cross D A; Watt P W; Downes C P
CORPORATE SOURCE:    Department of Biochemistry, Medical Sciences Institute,
                     University of Dundee, DD1 4HN Dundee, United Kingdom..
                     jvdkaay@bad.dundee.ac.uk
SOURCE:              JOURNAL OF BIOLOGICAL CHEMISTRY, (1997 Feb 28)
                     272 (9) 5477-81.
                     Journal code: HIV. ISSN: 0021-9258.
PUB. COUNTRY:        United States
                     Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:            English
FILE SEGMENT:        Priority Journals; Cancer Journals
ENTRY MONTH:         199706
AB   The pivotal role of phosphatidylinositol 3-kinase (PI 3-kinase) in signal
     transduction has been well established in recent years.
Receptor-regulated
     forms of PI 3-kinase are thought to phosphorylate phosphatidylinositol
     4,5-bisphosphate (PtdIns(4,5)P2) at the 3-position of the inositol ring
to
     give the putative lipid second messenger, phosphatidylinositol
     3,4,5-trisphosphate (PtdIns(3,4, 5)P3). Cellular levels of
PtdIns(3,4,5)P3
     are currently measured by time-consuming procedures involving
     radiolabeling with high levels of 32PO4, extraction, and multiple
     chromatography steps. To avoid these lengthy and hazardous procedures,
     many laboratories prefer to assay PI 3-kinase activity in cell extracts
     and/or appropriate immunoprecipitates. Such approaches are not readily
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applied to measurements of PtdIns(3,4,5)P3 in extracts of animal tissues. Moreover, they can be misleading since the association of PI 3-kinases in molecular complexes is not necessarily correlated with the enzyme's activity state. Direct measurements of PtdIns(3,4,5)P3 would also be desirable since its concentration may be subject to additional control mechanisms such as activation or inhibition of the phosphatases responsible for PtdIns(3,4,5)P3 metabolism. We now report a simple, reproducible isotope dilution assay which detects PtdIns(3,4,5)P3 at subpicomole sensitivity, suitable for measurements of both basal and stimulated levels of PtdIns(3,4,5)P3 obtained from samples containing approximately 1 mg of cellular protein. Total lipid extracts, containing PtdIns(3,4,5)P3, are first subjected to alkaline hydrolysis which results in the release of the polar head group Ins(1,3,4,5)P4. The latter is measured by its ability to displace [32P]Ins(1,3,4,5)P4 from a highly specific binding protein present in cerebellar membrane preparations. We show that this assay solely detects PtdIns(3,4,5)P3 and does not suffer from interference by other compounds generated after alkaline hydrolysis of total cellular lipids. Measurements on a wide range of cells, including rat-1 fibroblasts, 1321N1 astrocytoma cells, HEK 293 cells, and rat adipocytes, show wortmannin-sensitive increased levels of PtdIns(3,4,5)P3 upon stimulation with appropriate agonists. The enhanced utility of this procedure is further demonstrated by measurements of PtdIns(3,4,5)P3 levels in tissue derived from whole animals. Specifically, we show that stimulation with insulin increases PtdIns(3,4,5)P3 levels in rat skeletal muscle in **vivo** with a time course which parallels the activation of **protein kinase B** in the same samples.

L13 ANSWER 2 OF 11 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 97375495 MEDLINE
DOCUMENT NUMBER: 97375495
TITLE: A constitutively active version of the Ser/Thr kinase **Akt** induces production of the ob gene product, leptin, in 3T3-L1 adipocytes.
AUTHOR: Barthel A; Kohn A D; Luo Y; Roth R A
CORPORATE SOURCE: Department of Molecular Pharmacology, Stanford University School of Medicine, CA 94305-5332, USA.
CONTRACT NUMBER: DK 34926 (NIDDK)
5T32 DK07217-21 (NIDDK)
5T32 GM07365 (NIGMS)
SOURCE: ENDOCRINOLOGY, **(1997 Aug)** 138 (8) 3559-62.
Journal code: EGZ. ISSN: 0013-7227.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals
ENTRY MONTH: 199710

AB The expression of the ob gene product leptin in adipose tissues has been previously described to be regulated by insulin in **vivo** and vitro. **Akt**, a ser/thr kinase with a pleckstrin homology domain, has recently been identified to function in the insulin receptor signaling cascade. The aim of this study was to investigate the role of **Akt** in the production of leptin by adipocytes. Therefore, we examined leptin production by 3T3-L1 adipocytes stably expressing a myristoylated version of **Akt** which is constitutively active. Leptin levels in the supernatants of serum starved, nonstimulated 3T3-L1 adipocytes were determined by radioimmunoassay (RIA). Expression of the constitutively

active **Akt** was found to induce a more than 20-fold increase in leptin levels whereas a control non-myristoylated **Akt** had no effect. Leptin mRNA levels as determined by either RNase protection assay or reverse transcriptase (RT)-polymerase chain reaction (PCR) were not elevated by the constitutively active **Akt**. These results indicate that **Akt** can induce leptin production in 3T3-L1 adipocytes via a non-transcriptional mechanism.

L13 ANSWER 3 OF 11 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 1998055318 MEDLINE
DOCUMENT NUMBER: 98055318
TITLE: Growth factor stimulation of hematopoietic cells leads to membrane translocation of AKT1 protein kinase [see comments].
COMMENT: Comment in: Leuk Res 1997 Nov-Dec;21(11-12):1027-31
AUTHOR: Zhang X; Vik T A
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, Indiana University School of Medicine, Indianapolis 46202, USA.
SOURCE: LEUKEMIA RESEARCH, **(1997 Sep)** 21 (9) 849-56. Journal code: K9M. ISSN: 0145-2126.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Cancer Journals; Priority Journals
ENTRY MONTH: 199803
AB AKT1 is the human homolog of the v-**akt** oncogene. AKT1 has two distinct protein domains, one serine/threonine kinase domain and one pleckstrin homology (PH) domain. We studied the expression and activity of AKT1 in hematopoietic cell lines. The expression of AKT1 was constitutive in hematopoietic cells of various stages of development. In the growth factor dependent MO7e cells, serum and growth factor starvation resulted in an early 50% fall in activity which was maintained over 24 h. Treatment of cells which growth factors or agents which induce differentiation activated AKT1. The subcellular localization of AKT1 in MO7e cells was altered as it was activated. High AKT1 kinase activity was associated with membrane fractions in stimulated cells, in contrast to the much lower AKT1 activity in membranes of cells starved of serum and growth factor for 1 h. These results demonstrate AKT1 kinase activity and its regulation by extracellular signaling factors in **vivo** in hematopoietic cells, and suggest that the activation of AKT1 involves intracellular translocation of the kinase from cytosol to membrane.

L13 ANSWER 4 OF 11 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 1998022383 MEDLINE
DOCUMENT NUMBER: 98022383
TITLE: Interleukin-3-induced phosphorylation of BAD through the protein kinase **Akt**.
AUTHOR: del Peso L; Gonzalez-Garcia M; Page C; Herrera R; Nunez G
CORPORATE SOURCE: Department of Pathology and Comprehensive Cancer Center, University of Michigan Medical School, Ann Arbor, MI 48109, USA.
CONTRACT NUMBER: CA-64556 (NCI)
SOURCE: SCIENCE, **(1997 Oct 24)** 278 (5338) 687-9.

Journal code: UJ7. ISSN: 0036-8075.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199801
ENTRY WEEK: 19980104
AB BAD is a distant member of the Bcl-2 family that promotes cell death. Phosphorylation of BAD prevents this. BAD phosphorylation induced by interleukin-3 (IL-3) was inhibited by specific inhibitors of phosphoinositide 3-kinase (PI 3-kinase). **Akt**, a survival-promoting serine-threonine protein kinase, was activated by IL-3 in a PI 3-kinase-dependent manner. Active, but not inactive, forms of **Akt** were found to phosphorylate BAD in **vivo** and in vitro at the same residues that are phosphorylated in response to IL-3. Thus, the proapoptotic function of BAD is regulated by the PI 3-kinase-**Akt** pathway.

DUPLICATE 5

L13 ANSWER 5 OF 11 MEDLINE
ACCESSION NUMBER: 97158492 MEDLINE
DOCUMENT NUMBER: 97158492
TITLE: Direct regulation of the **Akt** proto-oncogene product by phosphatidylinositol-3,4-bisphosphate [see comments].
COMMENT: Comment in: Science 1997 Jan 31;275(5300):628-30
AUTHOR: Franke T F; Kaplan D R; Cantley L C; Toker A
CORPORATE SOURCE: ABL-Basic Research Program, National Cancer Institute-Frederick Cancer Research Facility and Development Center (NCI-FCRFDC), Frederick, MD 21702, USA..
tfranke@bidmc.harvard.edu
CONTRACT NUMBER: N01-CO-74101 (NCI)
GM41890 (NIGMS)
SOURCE: SCIENCE, **(1997 Jan 31)** 275 (5300) 665-8.
Journal code: UJ7. ISSN: 0036-8075.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199704
AB The regulation of the serine-threonine kinase **Akt** by lipid products of phosphoinositide 3-kinase (PI 3-kinase) was investigated. **Akt** activity was found to correlate with the amount of phosphatidylinositol-3,4-bisphosphate (PtdIns-3,4-P2) in **vivo**, and synthetic PtdIns-3,4-P2 activated **Akt** both in vitro and in **vivo**. Binding of PtdIns-3,4-P2 occurred within the **Akt** pleckstrin homology (PH) domain and facilitated dimerization of **Akt**. **Akt** mutated in the PH domain was not activated by PI 3-kinase in **vivo** or by PtdIns-3, 4-P2 in vitro, and it was impaired in binding to PtdIns-3,4-P2. Examination of the binding to other phosphoinositides revealed that they bound to the **Akt** PH domain with much lower affinity than did PtdIns-3,4-P2 and failed to increase **Akt** activity. Thus, **Akt** is apparently regulated by the direct interaction of PtdIns-3,4-P2 with the **Akt** PH domain.

DUPLICATE 6

L13 ANSWER 6 OF 11 MEDLINE
ACCESSION NUMBER: 1998004226 MEDLINE
DOCUMENT NUMBER: 98004226
TITLE: **Akt** phosphorylation of BAD couples survival

signals to the cell-intrinsic death machinery.

AUTHOR: Datta S R; Dudek H; Tao X; Masters S; Fu H; Gotoh Y; Greenberg M E

CORPORATE SOURCE: Children's Hospital and Department of Neurobiology, Harvard Medical School, Boston, Massachusetts 02115, USA.

CONTRACT NUMBER: NS28829 (NINDS)
GM53165 (NIGMS)
P30-HD 18655 (NICHD)

SOURCE: CELL, **(1997 Oct 17)** 91 (2) 231-41.
Journal code: CQ4. ISSN: 0092-8674.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199801
ENTRY WEEK: 19980104

AB Growth factors can promote cell survival by activating the phosphatidylinositide-3'-OH kinase and its downstream target, the serine-threonine kinase **Akt**. However, the mechanism by which **Akt** functions to promote survival is not understood. We show that growth factor activation of the PI3'K/**Akt** signaling pathway culminates in the phosphorylation of the BCL-2 family member BAD, thereby suppressing apoptosis and promoting cell survival. **Akt** phosphorylates BAD in vitro and in **vivo**, and blocks the BAD-induced death of primary neurons in a site-specific manner. These findings define a mechanism by which growth factors directly inactivate a critical component of the cell-intrinsic death machinery.

DUPLICATE 7

L13 ANSWER 7 OF 11 MEDLINE
ACCESSION NUMBER: 97133284 MEDLINE
DOCUMENT NUMBER: 97133284
TITLE: Mechanism of activation of **protein kinase B** by insulin and IGF-1.

AUTHOR: Alessi D R; Andjelkovic M; Caudwell B; Cron P; Morrice N; Cohen P; Hemmings B A

CORPORATE SOURCE: MRC Protein Phosphorylation Unit, Department of Biochemistry, University of Dundee, UK.

SOURCE: EMBO JOURNAL, **(1996 Dec 2)** 15 (23) 6541-51.
Journal code: EMB. ISSN: 0261-4189.

PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199704

AB Insulin activated endogenous **protein kinase B** alpha (also known as RAC/**Akt** kinase) activity 12-fold in L6 myotubes, while after transfection into 293 cells PKBalpha was activated 20- and 50-fold in response to insulin and IGF-1 respectively. In both cells, the activation of PKBalpha was accompanied by its phosphorylation at Thr308 and Ser473 and, like activation, phosphorylation of both of these residues was prevented by the phosphatidylinositol 3-kinase inhibitor wortmannin. Thr308 and/or Ser473 were mutated to Ala or Asp and activities of mutant PKBalpha molecules were analysed after transfection into 293 cells. The activity of wild-type and mutant PKBalpha was also measured in vitro after stoichiometric phosphorylation of Ser473 by MAPKAP kinase-2. These experiments demonstrated that activation of PKBalpha by insulin or insulin-like growth factor-1 (IGF-1) results from

phosphorylation of both Thr308 and Ser473, that phosphorylation of both residues is critical to generate a high level of PKBalpha activity and that the phosphorylation of Thr308 in **vivo** is not dependent on phosphorylation of Ser473 or vice versa. We propose a model whereby PKBalpha becomes phosphorylated and activated in insulin/IGF-1-stimulated cells by an upstream kinase(s).

DUPLICATE 8

L13 ANSWER 8 OF 11 MEDLINE
ACCESSION NUMBER: 88171297 MEDLINE
DOCUMENT NUMBER: 88171297
TITLE: Thymic lymphoma induction by the AKT8 murine retrovirus.
AUTHOR: Staal S P; Hartley J W
CORPORATE SOURCE: Johns Hopkins Oncology Center, Baltimore, Maryland 21205.
CONTRACT NUMBER: NO1-AI-22673 (NIAID)
SOURCE: JOURNAL OF EXPERIMENTAL MEDICINE, **(1988 Mar 1)** 167 (3) 1259-64.
Journal code: I2V. ISSN: 0022-1007.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 198807

AB The directly transforming murine retrovirus, AKT8, was isolated from a spontaneous AKR thymoma and carries the cell-derived viral oncogene, **akt**. We have now shown that this virus produces thymic lymphomas after inoculation of susceptible mouse strains. The presence of the AKT8 genome in the DNA of the virus-induced tumors was demonstrated by Southern blotting using an **akt**-specific probe. These results establish the in **vivo** pathogenicity of the AKT8 virus and its **akt** oncogene, and imply a potential role for the cellular **akt** proto-oncogene in tumor development.

L13 ANSWER 9 OF 11 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1989:3871 BIOSIS
DOCUMENT NUMBER: BA87:3871
TITLE: MOLECULAR MECHANISM OF THE INHIBITORY EFFECTS OF ISOQUINOLINESULFONAMIDES ON PROTEIN KINASES.
AUTHOR(S): HAGIWARA M
CORPORATE SOURCE: DEP. PHARMACOL., NAGOYA UNIV. SCH. MED., SHOWA-KU, NAGOYA 466, JPN.
SOURCE: MIE MED J, (1988) 38 (2), 137-154.
CODEN: MMJJAI. ISSN: 0026-3532.
FILE SEGMENT: BA; OLD
LANGUAGE: English

AB Molecular properties of MLC-kinase, protein kinase C, and cAMP-dependent protein kinase were analysed using selective inhibitors of isoquinolinesulfonamide derivatives. These protein kinases were potently inhibited by 1-(8-chloro-5-isoquinolinesulfonyl) piperazine (HA-156) and its derivatives. Kinetic analysis indicated that HA-156 inhibited both enzymes competitively with respect to ATP, and ki values of HA-156 for MLC-kinase and protein kinase C were 7.3 and 7.2 .mu.M, respectively. To clarify molecular mechanisms of the isoquinolinesulfonamides to inhibit the Ca2+-dependent protein kinases, the structure-activity relationships of HA-156 and its derivatives were examined. The dechlorinated analogues, HA-100 and HA-142, markedly decreased the affinity for MLC-kinase, suggesting that the inhibitory effect of isoquinolinesulfonamide derivatives depends upon the hydrophobicity of the compounds. There is a good correlation between MLC-kinase inhibition and hydrophobicity

determined by reverse phase chromatography. In contrast, HA-140 and HA-142 showed weak inhibition of protein kinase C, suggesting that the electron density of the nitrogen in the isoquinoline ring of the compounds correlates with the potency to inhibit protein kinase C activity. When the piperazine ring was replaced by the methylaminoethyl chain, the compound, named H-8, specifically inhibited cyclic nucleotide dependent protein kinases and did not affect Ca2+-dependent enzymes. The interaction of H-8 with the catalytic subunit of cAMP-dependent protein kinase was studied, using various affinity labeling reagents of the ATP binding site of the purified protein kinase catalytic subunit and the gelpermeation binding assay. The data showed that H-8 specifically binds to the ATP binding site of the catalytic subunit with a binding ratio of 1:1 and that H-8 has unique features which differ from the ATP analogues, in the following points: a) H-8, among other protein kinases or ATP utilizing enzymes, specifically inhibits cyclic nucleotide-dependent **protein kinase; b**) the binding constant (Km) of H-8 to the enzyme is much lower than that of ATP; c) the binding of H-8 to the enzyme is independent of magnesium ion; d) the binding subsite of H-8 at the active site of the enzyme slightly differs from that of ATP. These isoquinolinesulfonamide derivatives should prove to be useful tools for distinguishing the role of each protein kinase, in **vivo**.

L13 ANSWER 10 OF 11 CANCERLIT
ACCESSION NUMBER: 75703843 CANCERLIT
DOCUMENT NUMBER: 75703843
TITLE: SPONTANEOUS AKR LYMPHOMA WITH T AND B-CELL CHARACTERISTICS.
AUTHOR: Greenberg R S; Zatz M M
CORPORATE SOURCE: Natl. Cancer Inst., Bethesda, Md. 20014.
SOURCE: Nature, **(1975)**. Vol. 257, No. 5524, pp. 314-316. ISSN: 0028-0836.
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
FILE SEGMENT: CARC
LANGUAGE: English
ENTRY MONTH: 197606

AB Lymph nodes and spleens from AKR/J mice bearing the passaged AkTB-1 tumor line, derived from a spontaneous lymphoma in lymph nodes and spleen of a thymectomized AKR/J mouse, were examined for the presence of Thy1.1 antigen by an indirect specific-immunofluorescent staining technique. Spleen or lymph node cells were incubated with anti-Thy1.1 antiserum prepared by hyperimmunization of CBA/J mice with **AKT**/J thymocytes. By day 12 of passage, more than 90% of lymph node and spleen cells were Thy1.1-positive. Similar results were obtained with cells from AKR mice bearing a spontaneous thymoma or another passaged AKR lymphoma cell line derived from a spontaneous AKR/J thymoma. Late in passage almost all AkTB-1 spleen cells, but few lymph node cells, bore both IgM and Thy1.1 on their surfaces. Since the coexistence of T- and B-cell markers on the same cell is unusual, the possibility that either Thy1.1 or surface IgM was passively acquired was investigated. Late passage AkTB-1 spleen cells were capped by incubation with unlabeled anti-Thy1.1 serum at 30 min at 4 C, followed by incubation with unlabeled anti-mouse gamma2 heavy chain antibody for one hour at 37 C. Cells having IgM were similarly

capped, but with a single incubation with unlabeled anti-mouse Ig. As shown by subsequent staining with fluorescein-conjugated anti-gamma2, Thy1.1 and IgM caps formed immediately after incubation were neither shed nor redistributed over the cell surface following overnight incubation. These results suggest that AkTB-1 spleen cells can generate Th1.1 antigen and surface IgM. Late in passage, when AkTB-1 spleen cells were 95% Th1.1- and 83% IgM-positive, they exhibited elevated spontaneous DNA synthesis that was depressed by phytohemagglutinin (PHA) but markedly stimulated by lipopolysaccharide (LPS). These results further support the dual nature of the spleen cells because LPS responsiveness appears to be a characteristic of B cells, whereas PHA-induced inhibition of DNA synthesis is reportedly a characteristic of some murine T-cell lymphoma lines. The progressive acquisition of B-cell characteristics by AkTB-1 cells, as well as their differential expression in spleen and lymph nodes, suggest that these cells undergo differentiation in **vivo**; and that the lymphoid tissue microenvironment has a role in the control of this differentiation process.

L13 ANSWER 11 OF 11 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 75000744 EMBASE
DOCUMENT NUMBER: 1975000744
TITLE: Effect of 18 hr fast and glutathione depletion on 1,1 dichloroethylene induced hepatotoxicity and lethality in rats.
AUTHOR: Jaeger R.J.; Conolly R.B.; Murphy S.D.
CORPORATE SOURCE: Dept. Physiol., Kresge Cent. Environm. Hlth, Harvard Sch. Publ. Hlth, Boston, Mass. 02115, United States
SOURCE: Experimental and Molecular Pathology, (1974) 20/2 (187-198).
CODEN: EXMPA6
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
005 General Pathology and Pathological Anatomy
030 Pharmacology
LANGUAGE: English
AB Four hr inhalation exposure to 1,1 dichloroethylene (1,1 DCE, vinylidene chloride) was more injurious to 18 hr (overnight) fasted rats than to rats fed ad libitum. The estimated 24 hr LC50 for fed rats was 15,000 ppm while the same value for fasted rats was 600 ppm. The minimum lethal concentration was 200 ppm for fasted rats and 10,000 ppm for fed rats. Serum alanine .alpha. ketoglutarate transaminase (**AKT**) elevation occurred at 150 ppm in fasted rats, but in the fed rats, a significant elevation was only seen at 2000 ppm and higher. Elevated serum **AKT** preceded hepatic necrosis and death. This fed fasted difference in serum **AKT** elevation was also demonstrable in an isolated perfused rat liver system. The **AKT** elevation in perfusate from livers of fasted rats was consistent with the time course of injury seen in **vivo**. Increased susceptibility to hepatic injury appeared to be related to decreased hepatic glutathione concentration associated with fasting (18 hr). Diethylmaleate, a material which results in a decreased hepatic glutathione concentration was administered in **vivo** and in vitro. This treatment potentiated the hepatic injury in fed rats and in livers taken from fed rats and subsequently perfused.